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ORIGINAL ARTICLE

Biliary complications including single-donor mortality: experience of 207 adult-to-adult living donor liver transplantations with right liver grafts

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Abstract

Background: After right lobe donation, biliary complication is the main cause of morbidity. Mortality after right lobe donation has been estimated to be less than 0.5%.

Patients and methods: Between November 2001 and December 2008, 207 adult-to-adult living donor liver transplantations (ALDLT) were undertaken using right lobe grafts. Donors included 173 men and 34 women with a mean age of 28.4 ± 5.2 years.

Results: Siblings comprised 144 (69.6%) cases whereas unrelated donors comprised 63 (30.4%) with a mean body mass index (BMI) of 25.2 ± 2.4. Single and multiple right hepatic ducts (RHD) were present in 82 (39.6%) and 125 (60.3%) donors, respectively. Mean operative time was 360 ± 50 min with an estimated blood loss of 950 ± 450 ml and returned cell-saver amount of 450 ± 334 ml. Mean donor remnant liver volume was 33.5 ± 3.2%. Mean intensive care unit (ICU) stay was 3 ± 0.7 days and mean hospital stay was 14 ± 3.5 days. Modified Clavien classifications were used to stratify all donor biliary complications The overall biliary complications occurred in 27 cases (13.0%). After modified Clavien classification, biliary complications were graded as grade I (n = 10), grade II (n = 2), grade III (n = 14) and grade V (n = 1). Grade I and II (n = 12) biliary complications were successfully managed conservatively. Grade III cases were treated using ultrasound-guided aspiration (USGA), endoscopic retrograde cholangiography (ERCP) and surgery in 10, 2 and 2 donors, respectively. Single donor mortality (Grade V) (0.4%) occurred after uncontrolled biliary leakage with peritonitis that necessitated exploration followed by ERCP with stent insertion but the donor died on day 43 as a result of ongoing sepsis.

Conclusion: Although the majority of biliary complications are minor and can be managed conservatively, uncontrolled biliary leakage is a serious morbidity that should be avoided as it could lead to mortality.

Keywords

biliary complications, donors, liver transplant

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Introduction

Since 2001, adult-to-adult living donor liver transplantation (ALDLT) has been the only available treatment with curative intent for patients with end-stage liver disease (ESLD) in Egypt.[1,2] There is an absence of a deceased donor transplant programme as a result of the ongoing debate around brain stem death and the issuing of a comprehensive transparent organ transplant law. The concerns that patients have only one chance with an equivalent graft and patient survivals together with the challenges of donor

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risk adds to the complexity of the situation. Biliary anomalies are more common in right liver (RLG) compared with left liver grafts (LLG).[3,4] Large stature Egyptian patients almost always impose the need for RLG harvesting compared with the Far East where LLG are often used.[5,6] Biliary complications are the main cause of morbidity after right-sided donation.[7] Unresolved biliary complications may lead to sepsis, multi-organ failure (MOF) and death. Mortality after right lobe donation has been estimated to be less than 0.5%. This report documents biliary complications including a single mortality in the first 207 RLG living donors.

Patients and methods

Study population

From November 2001 to December 2008, 207 ALDLT procedures were undertaken for patients with ESLD and/or hepatocellular carcinoma (HCC). RLG were harvested, in all donors, either with (n = 30) or without (n = 177) the middle hepatic vein (MHV). Demographic data of the study population included 173 males and 34 females with s age range between 18 and 50 years. The mean age of all donors was 28.4 ± 5.2 years. Only donors with a maximum body mass index (BMI) ≤ 28 was accepted and assessed for donation. The mean BMI was 25.2 ± 2. Accepted criteria of live donation were met within a family member in 144 (69.6%) donors whereas the remaining 63 (30.4%) cases could not identify a reasonable sibling for donation and received a RLG from an unrelated friend. The three-steps donor preparation protocol has been reported elsewhere.[2] Liver biopsy is a routine practice in donor preparation and macrovesicular steatosis is only accepted if it is between 0 and 15% with the total absence of any portal inflammation.

Psychosocial assessment by an experienced informed psychiatrist is an integral step in donor preparation to exclude any coercion and ensure altruism.

Informed consent was obtained from all donors after making sure that they fully understood the procedure details, possible risks and complications as well as all the short-term post-operative financial implications resulting from a period of sick leave of the order of 6–8 weeks.

Ethics

The hospital ethical committee has to review all patient and donor files and meet with either the donor or recipient before approving donation. A separate donor advocate team was instituted recently and has started to revise donor assessment and defend all donor rights of being fully informed at all times.

Operative technique

The detailed operative technique for RLG harvesting without inclusion of the MHV has been described elsewhere.[2] The Hong Kong technique[8] of harvesting RLG with MHV was adopted whenever the decision was to proceed with this technique (n = 30). All procedures were done and/or supervised by one of the first two authors. The technique of tackling the right hepatic duct (RHDs) included: routine intra-operative cholangiogram, keeping peri-ductal dissection to the minimum followed by sharp transection of RHDs before starting parenchymal transection. The hilar plate is divided and suture ligated using 5/0 prolene on both sides. RHDs stumps, kept at 2–3 mm from the junction between common hepatic duct (CHD) and left hepatic duct (LHD), are closed by interrupted 6/0 PDS. Biliary leakage from the closed stump or from the transection margin is tested twice by saline injection into the cystic duct catheter immediately after stump closure and after graft harvesting. Routine conclusion cholangiogram to visualize the left biliary system and document absence of any leakage or ductal stenosis is the last step in the donor operation.

Cell saver (Dedico, Electa; Sorin group, Mirandola, Italy) is routinely used in all donor operations. Prophylaxis against thromboembolism is offered to all donors when the prothrombin concentration reaches 50% and kept for 4 weeks on a single subcutaneous (s.c.) daily dose of enoxparine 40 mg /day.

In an effort to decrease the incidence of biliary complication, bilirubin content in drain effluent is routinely measured, if any doubt exists until bilirubin content is less than the serum bilirubin level. Minor bile leaks are monitored carefully as this usually settles spontaneously; however, if it becomes symptomatic by clinical and/or laboratory measures, an abdominal CT scan and/or MRC is immediately done. Having the full data of a given donor, an elaborate discussion is made between the experienced surgeon, endoscopist and an interventional radiologist aiming at reaching a consensus decision on what would be the appropriate intervention whether ultrasound-guided aspiration, endoscopic retrograde cholangiography (ERCP), percutaneous transhepatic dilatation (PTD) or surgery. Cases treated by ultrasound-guided aspiration and insertion of a pig-tail catheter were followed by abdominal ultrasound. The decision to remove the pig-tail was taken when the draining amount was less than 50 ml/day for 2 successive days with abdominal ultrasound documenting complete disappearance of any abdominal collection.

Follow-up plan

After discharge, all donors are followed at the out-patient clinic every week for 1 month to ensure a normal liver profile and to assess a comparative CT volumetry by a senior surgeon. Thereafter, donors are seen once every month or every 3 months for 2 years according to the presence or not of biliary complications. Donors are informed to return if they have any complaints or abnormalities at any point during the whole follow-up period.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous data were expressed as mean (SD). To study the impact of the number of the right bile ducts on the incidence of biliary complications, Fisher's exact test was used. SPSS v. 15.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for data analysis.

Results

The mean operative time was 360 ± 50 min with a mean blood loss of 950 ± 450 ml. No autologus or allogenic blood is prepared for live liver donors. The mean amount of cell saver blood was 443 ± 334 ml. Two cases (0.9%) were re-operated for bleeding and received two units of allogenic packed red blood cells (RBCs) each.

Graft data

The donor mean total liver volume was 1324.3 ± 187.1 g. The mean graft-recipient body weight ratio (GRWR) was 1.1 ± 0.3% whereas the mean donor remnant liver volume (RLV) was 473.8 ± 97.5 g which was equivalent to 34.5 ± 3.2% of the donor's total liver volume. Single and multiple RHD were present in 82 (39.6%) and 125 (60.3%) donors, respectively. Multiple RHD included 2 or 3 RHD in 116 (56%) and 9 (4.3%) cases, respectively.

Hospital stay

The mean intensive care unit (ICU) stay was 3 ± 0.7 days whereas the mean hospital stay was 13.5 ± 3.3 days. The follow-up period ranged from 3 to 86 months with a mean of 46 ± 4.3 months.

Donor complications: were graded according to the modified Clavien classification[9] of surgical complications. In the whole study population, the overall complications was 28.5% (n = 59) with biliary complications alone constituting 13.0% (27 cases). All types of donor complications after Clavien classification are shown in Fig. 1.

Biliary complications (Table 1): Twenty-seven donors (13.04%) suffered biliary complications. Within these 27 donors, the RHD was single in 12 (14%) and multiple in 15 (12%) being double in 14 and triple in a single donor (P = 0.72). Biliary complications were separately graded, according to modified Clavien classification,[9,10] as grade I (n = 10, 37%), grade II (n = 2, 0.07%), grade III (n = 14, 51%), grade IV (n = 0) and grade V (n = 1). Grade III were sub-divided into grade III a (n = 10) and grade III b (n = 4). The 10 cases that fell within grade I included minor biliary leaks and prolonged drainage time than usual with resultant prolonged hospitalization. Two grade II donors received additional antibiotic therapy after finishing the protocol-based prophylactic regimen in response to fever and rigours and guided by the draining effluent culture and sensitivity.

Grade III a/b biliary complications

The 14 grade III donors had biliary leaks in 13 cases and biliary stricture in a single case (Fig. 2). This group was further divided according to the type of management into grade III a (n = 10) and grade III b (n = 4).

Ten grade IIIa donors had symptomatic sub-phrenic biliary collection of different sizes and all 10 donors within this grade were managed successfully using ultrasound-guided aspiration and pig-tail tube drainage. The draining tube was left for a period that ranged from 1 to 3 weeks and then removed without any further intervention.

Grade IIIb donor complications were managed by ERCP and surgery in two patients, respectively. Prolonged sub-phrenic biliary collections that did not resolve by USGA in two patients was dealt with successfully by ERCP and insertion of a 10-F stent. Surgical management was resorted to in two donors; one by T-tube insertion after failure of ERCP to control the leak. After 1 month, a normal control cholangiogram was followed by removal of the T-tube. Two months later, an elevated total bilirubin and mild intra-hepatic biliary dilatation prompted ERCP and stent

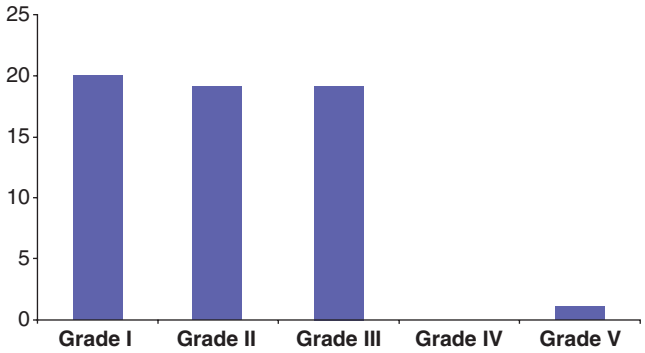

Figure 1 Donor complications according to the modified Clavien classification

Table 1 Biliary complications according to the modified Clavien classification

Grade of complication	Biliary complication	Treatment	Outcome
Grade I (n = 10)	Minor biliary leak; prolonged drainage time/ hospitalization	No	Alive
Grade II (n = 2)	Mild controlled sepsis	Antibiotics	Alive
Grade III a (Local anaesthesia) (n = 10)	Symptomatic sub-phrenic collection	USGA.	Alive
Grade III b (General anaesthesia) (n = 4)	Prolonged sub-phrenic collection – Excessive bile leak, failure of ERCP – Accidental CHD transaction	ERCP (n = 2) Surgery (n = 2)	Alive
Grade IV (n = 0)	–	–	–
Grade V (n = 1)	Uncontrolled bile leak, uncontrolled sepsis	Surgery/ERCP	Death
Total: n = 27 (13.04%)			27 (13.04%)

USGA, ultrasound guided aspiration; CHD, common hepatic duct; ERCP, endoscopic retrograde cholangio pancreatography.

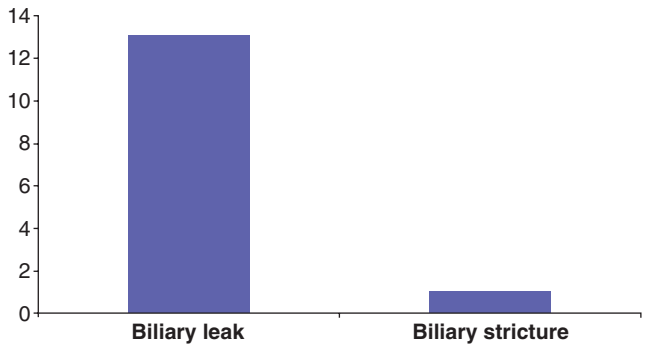

Figure 2 Grade III biliary complications

insertion to deal with a stricture at the LHD and CHD junction. A second patient that required surgery underwent LHD to CHD anastomosis over a 6-F biliary stent after accidental CHD transection during the index donor operation. The biliary stent was removed after 1 month but anastomotic stricture occurred 2 month later and was managed by PTD and stent insertion. Three months later, ERCP and stent replacement was performed but the stent was removed after another 3 months and has remained stent free. All grade III b donors are alive and back to their normal life and activities.

Grade V biliary complication

A single donor mortality (0.4%) occurred. This was donor number 32 who was a 44-year-old male with a BMI of 28 and was donating to his brother, with no documented co-morbidity and a liver biopsy that revealed 5% steatosis. The donor surgery was uneventful and lasted 330 min with 630 ml blood loss and a single RHD stump that was closed with 6/0 PDS in a continuous fashion. Total liver volume was 1340 g and the RLV was 480 g (35.8%). A biliary leak was declared on post-operative day 5 and was thought to be well drained but the patient developed biliary peritonitis necessitating exploration on day 11. The RHD stump was found to be the source of leakage. Peritoneal toilet and closure of the leaking site by interrupted PDS 6/0 was performed followed by draining all abdominal compartments. The patient did well for 10 days but then became more septic when biliary leak recurred and increased such that re-exploration on day 31 was undertaken. The abdominal cavity was found to be clean and the site of leakage was well drained by the remaining drains. Full left liver regeneration had occurred precluding easy access to the leaking site. The ongoing bile leak led to the decision to perform ERCP on day 38, in a an attempt to seal the leaking site. Repeat cultures from all body fluids and appropriate antibiotic therapy was continued through the post-operative course. However, the donor succumbed on day 43 as a result of uncontrolled sepsis and multi-organ failure. An autopsy was not done as this practice, although extremely useful, is rejected by our community. This case was reviewed in detail by the local ethical committee and the transplant team who were asked to hold the programme for one month and revise all steps included in the protocol including pre-operative, operative and post-operative measures.

Outcome

There were no deaths reported above and during a follow-up period that ranged between 3 and 84 months, all 26 donors who have had biliary complications are alive, and have gone back to their usual activities and are pursuing a normal life.

Discussion

ALDLT has gained popularity during the past decade because of the widening gap between the demand and supply of liver grafts from deceased donors in the West. The particular situation in Egypt has left little choice for ESLD patients and the transplant community but to accept LDLT. However, the fact remains that a substantial number of patients cannot identify a family member as an acceptable donor because of blood group incompatibility, age restriction, obesity or lack of the motivation to donate. In the present study, this group represented one-third of the study population (30.4%). We are aware of all the implications that this practice entails in a country where an organ transplant law has not yet seen the light. Making sure that every donor is fully aware of all likely operative and post-operative events and clearly informed by the unit's own results is regularly revised[11–13] A local ethical committee has had the responsibility of approving each case with its donor by setting realistic reasonable standards to ensure complete awareness of the donor and family about the procedure and document lack of coercion. Routine liver biopsy is practiced for two reasons; first, the high levels of obesity and steatotic livers and second, the bilharzial heritage although it is now fair to regard it as a vanishing problem.

Since the first successful ALDLT,[14] RLG has been regarded as the optimal graft for ESLD adult patients in terms of size, function and accommodation of the frequently high portal flow.[15] Although the feasibility of LLG in, small-sized, adult patients has been elegantly demonstrated,[6,16] we were unable to replicate this practice in our adult patients as the pre-operative volume calculation coupled with the frequent steatotic livers in Egypt almost always precluded LLG as an option for our adult patients. RLG represented the minimal requirement to cope with the metabolic needs, advanced disease status and severe portal hypertension in big stature Egyptian patients. After gaining enough experience, donors with dominant middle hepatic vein, who were refused before, started to be accepted by the end of 2006 where 30 RLG with MHV inclusion[8] have been done without reporting any morbidity in these donors.

In a systematic review including 131 studies, Middleton *et al.* reported donor morbidity ranging from zero to 100% with a median of 16.1%.[17] We are documenting an overall complication rate around 28.5%, 15% of which is non-biliary complications. The wide discrepancy in reported figures of complications could be explained by while some reports are concerned with severe may

be life-threatening complications[18] others mention all types of complications even the most trivial ones.[19,20] While the extent of liver segment donation, the learning curve effect and the observation period are important factors in this respect, the lack of a standardized universally accepted scale for documenting live liver donor complications is an important factor in the wide variation of reported complication rates. In the present study, we applied the modified Clavien classification[9] referring each and every complication to this classification with a total complication rate of 28.5%. Shah *et al.*[21] adopted the same principle, using the original Clavien classification of surgical complications,[10] and recorded an overall complication rate of 37%. Recently, Chan *et al.*[22] according to modified Clavien classification,[9] considered that the accepted overall morbidity rate in ALDLT should stay around 20%.

Right liver lobe anomalies, especially biliary anomalies, are common with the presence of multiple biliary orifices being a problem almost specific to RLG.[4,23] Biliary complications are the most common morbidity in living liver donors constituting some 0–38.6% with a median of 6.2%.[17] A low biliary complication rate of 2.4–5.3% has been reported after harvesting all types of liver grafts, right and left, together.[7,24] Considering biliary complications according to the type of the harvested graft, RLG donation yielded a higher biliary complication rate ranging from 10 to 12% compared with that after LLG donation which ranged from 2 to 4%.[16,24] In the current study, we had a slightly higher biliary complications rate of 13.4% mainly biliary leaks with a single case of biliary stricture. Minor biliary complications occurred in 12 (44.4%) out of the total 27 cases that had biliary complications, Clavien grade I or II, and needed no interventions at all. However, 14 cases (51.8%) were classified as Clavien grade III necessitating radiological/endoscopic intervention in 12 and surgical correction in 2 cases. Bile leak from the resection margin occurs in 5–10% of RLG donors.[25,26] All Clavien grade I, II and III A cases were biliary leaks of varying degree accounting for 81.4% ($n = 22$) of the total biliary complications in the current study. Considering the whole study population, this is equivalent to a 10.6% bile leak rate which is consistent with other reported studies.

Pre-operative donor evaluation and selection could be partly responsible for the more serious Clavien grade III B biliary complications. Sixty per cent of the presented donor population had multiple RHDs, a finding that is not commonly shared by other studies.[3,4] Considering that multiple, rather than single, RHDs might be a risk factor for donor biliary complications was not valid in this study as within the 27 donors who developed biliary complications 12 (14%) had single whereas 15 (12%) had more than one RHD **yielding a non-significant difference between the two groups.** Therefore, pre-operative identification of multiple RHDs was not rejected if the donor is proved to be otherwise fit for donation in all other aspects. This strategy could be further justified appreciating that the process of identifying a reasonable living liver donor has been always a painful task for the family.

Anatomically, excessive dissection of the right hepatic artery from behind the CHD could be responsible for some ischaemic effect resulting in increased bile leakage or stenosis following RLG compared to LLG harvesting.[16] Operatively, we transect the RHD(s) after operative cholangiography, full dissection of the right hepatic pedicle and before commencing parenchymal transection. We believe that this puts the left biliary system out of harms way and by suture ligation of the divided hilar plate on both sides, parenchymal transection is made more safe, rapid and easier. Alternatively, RHD division is performed by others either after transection of the anterior two-third[21,27] or at the conclusion of parenchymal transaction[28] with similar rates of biliary complications. Thus, the best timing of RHD division remains to be settled.

The majorty of biliary complications is managed by conservative or minimally invasive procedures such as USGA.[29] We managed 81.2% ($n = 22$) of our biliary complications successfully in a similar manner. Nevertheless, Clavien grade IIIB donors ($n = 4$) underwent major manipulation of their left bile duct system by ERCP in two cases and surgical correction in two cases. The latter two donors needed further management by PTD and ERCP with ballon dilatation and stent insertion in more than one setting. During donor surgery, iatrogenic biliary injury is one of the most dreadful complications. CHD was transected instead of RHD once in donor 137 that we can't reside on the learning curve effect as a reason for this type of complication. Meanwhile, the remaining three donors with grade IIIB complications occurred early on during the second and third year of the whole study period reflecting the learning curve effect. Although complete recovery was established in all four donors, the course has been long, worrying and temporary affected the donor moral. Major manipulation of the biliary system by PTD from above or ERCP from below is usual practice in recipients but is at least alarming in healthy donors. Lee *et al.* followed a similar strategy with an equivalent outcome.[29] To date, all Clavien grade IIIB donors are pursuing their life normally without recurrence during a mean follow-up period of 46 months.

Death of a healthy live donor is torturing to the responsible transplant team and the medical community at large. Regrettably, worldwide recorded live liver donor mortality is not regularly followed or updated to include all continents. This regretful event happened in 0.2–0.5% in most reported series.[11,30] After RLG donation, 0.5% mortality is the circulating figure.[11] This report documents a single donor mortality in a large series of 207 ALDLT, equivalent to 0.4%, as a result of ongoing uncontrolled sepsis with MOF stemming from major uncontrolled biliary leak. Identifying pre-operative or operative risk factors that could be responsible for RHD stump bile leak, in this case, was not possible except that we assumed that RHD stump closure in a continuous fashion should be replaced by an interrupted manner although there is no data to support this assumption. A standard protocol of dealing with early biliary complications, involving all expertise, has been followed since the occurrence of our tragic event.

In conclusion, in an effort of continuous documentation the current study is reporting on the most common morbidity after

live donation in ALDLT. Biliary complications are serious events in the post-operative setting as they may lead to mortality and therefore should be avoided by all means. Every aspect including donor selection, pre-operative preparation, operative technique and post-operative care, should be regularly revised and discussed in detail with the aim of fine tuning and adjusting this delicate practice.

Conflicts of interest

None declared

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